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L8: Entry 10 of 10 File: USPT Jan 12, 1999

DOCUMENT IDENTIFIER: US 5858776 A
TITLE: Tumor cells with increased immunogenicity and uses therefor

Detailed Description Text (38):
Another aspect of the invention provides methods for increasing the immunogenicity of a tumor cell by modification of the tumor cell in vivo to express a costimulatory molecule to trigger a costimulatory signal in T cells. In addition, tumor cells can be furtner modified in vivo to express MHC molecules to trigger a primary, antigen-specific, signal in T cells. Tumor cells can be modified in vivo by introducing a nucleic acid encoding a T cell costimulatory molecule into the tumor cells in a form suitable for expression of the costimulatory molecule on the surface of the tumor cells. Likewise, nucleic acids encoding MHC class I or class II molecules or an antisense sequence of the Ii gene can be introduced into tumor cells in vivo. In one embodiment, a recombinant expression vector is used to deliver nucleic acid encoding B7 to tumor cells in vivo as a form of gene therapy. Vectors useful for in vivo gene therapy have been previously described and include retroviral vectors, adenoviral vectors and adeno-associated viral vectors. See e.g. Rosenfeld, M. A., Cell 68, 143-155 (1992); Anderson, W. F., Science 226, 401-409 (1984); Friedman, T., Science 244, 1275-1281 (1989). Alternatively, nucleic acid can be delivered to tumor cells in vivo by direct injection of naked nucleic acid into tumor cells. See e.g. Acsadi, G., et al., Nature 332, 815-818 (1991). A delivery apparatus is commercially available (BioRad). Optionally, to be suitable for injection, the nucleic acid can be complexed with a carrier such as a liposome. Nucleic acid encoding an MHC class I molecule complexed with a liposome has been directly injected into tumors of melanoma patients. Hoffman, M., Science 256, 305-309 (1992).

L6: Entry 2 of 3 File: USPT May 21, 2002

DOCUMENT-IDENTIFIER: US 6391565 B2
TITLE: Methods of detecting growth differentiation factor-3

Priority Application Year (1):
1994

Detailed Description Text (7):
The invention provides polynucleotides encoding the GDF-3 protein. These polynucleotides include DNA, cDNA and RNA sequences which encode GDF-3. It is understood that all polynucleotides encoding all or a portion of GDF-3 are also included herein, as long as they encode a polypeptide with GDF-3 activity. Such polynucleotides include naturally occurring, synthetic, and intentionally manipulated polynucleotides. For example, GDF-3 polynucleotide may be subjected to site-directed mutagenesis. The polynucleotide sequence for GDF-3 also includes antisense sequences. The polynucleotides of the invention include sequences that are degenerate as a result of the genetic code. There are 20 natural amino acids, most of which are specified by more than one codon. Therefore, all degenerate nucleotide sequences are included in the invention as long as the amino acid sequence of GDF-3 polypeptide encoded by the nucleotide sequence is functionally unchanged.

Detailed Description Text (21):
Polynucleotide sequences encoding GDF-3 can be expressed in either prokaryotes or eukaryotes. Hosts can include microbial, yeast, insect and mammalian organisms. Methods of expressing DNA sequences having eukaryotic or viral sequences in prokaryotes are well known in the art. Biologically functional viral and plasmid DNA vectors capable of expression and replication in a host are known in the art. Such vectors are used to incorporate DNA sequences of the invention.

Detailed Description Text (23):
When the host is a eukaryote, such methods of transfection of DNA as calcium phosphate co-precipitates, conventional mechanical procedures such as microinjection, electroporation, insertion of a plasmid encased in liposomes, or virus vectors may be used. Eukaryotic cells can also be cotransformed with DNA sequences encoding the GDF-3 of the invention, and a second foreign DNA molecule encoding a selectable phenotype, such as the herpes simplex thymidine kinase gene. Another method is to use a eukaryotic viral vector such as simian virus 40 (SV40) or bovine papilloma virus, to transiently infect or transform eukaryotic cells and express the protein. (see for example, Eukaryotic Viral Vectors, Cold Spring Harbor Laboratory, Gluzman ed., 1982).

Detailed Description Text (26):
The term "cell-proliferative disorder" denotes malignant as well as non-malignant cell populations which often appear to differ from the surrounding tissue both morphologically and genotypically. The GDF-3 polynucleotide that is an antisense molecule is useful in treating malignancies of the various organ systems, particularly, for example, cells in the bone marrow, spleen, thymus or adipose tissue. Essentially, any disorder which is etiologically linked to altered expression of GDF-3 could be considered susceptible to treatment with a GDF-3 suppressing reagent. One such disorder of associated with bone marrow-derived cells is leukemia, for example. The term "immunologic disorder" refers to a disorder involving cells of the immune system, for example lymphocytes. Such immunologic disorders include disorders associated with the inflammatory process for example. The immunologic disorder is not limited to an immunologic cell proliferative disorder.

Detailed Description Text (39):
The present invention identifies a nucleotide sequence that can be expressed in an altered manner as compared to expression in a normal cell, therefore it is possible to design appropriate therapeutic or diagnostic techniques directed to this sequence. Thus, where a cell proliferative or immunologic disorder is associated with the expression of GDF-3, nucleic acid sequences that interfere with GDF-3 expression at the translation level can be used. This approach utilizes, for example, antisense nucleic acid and ribozymes to block translation of a specific GDF-3 mRNA, either by masking that mRNA with an antisense nucleic acid or by cleaving it with a ribozyme.

Detailed Description Text (40):
Antisense nucleic acids are DNA or RNA molecules that are complementary to at least a portion of a specific mRNA molecule (Weintraub, Scientific American, 262:40, 1990). In the cell, the antisense nucleic acids hybridize to the corresponding mRNA, forming a double-stranded molecule. The antisense nucleic acids interfere with the translation of the mRNA, since the cell will not translate a mRNA that is double-stranded. Antisense oligomers of about 15 nucleotides are preferred, since they are easily synthesized and are less likely to cause problems than larger molecules when introduced into the target GDF-3-producing cell. The use of antisense methods to inhibit the in vitro translation of genes is well known in the art (Marcus-Sakura, Anal.Biochem., 172:289, 1988).

Detailed Description Text (43):
The present invention also provides gene therapy for the treatment of cell proliferative or immunologic disorders which are mediated by GDF-3 protein. Such therapy would achieve its therapeutic effect by introduction of the GDF-3 antisense polynucleotide into cells having the proliferative disorder. Delivery of antisense GDF-3 polynucleotide can be achieved using a recombinant expression vector such as a chimeric virus or a colloidal dispersion system. Especially preferred for therapeutic delivery of antisense sequences is the use of targeted liposomes.

Detailed Description Text (44):
Various viral vectors which can be utilized for gene therapy as taught herein include adenovirus, herpes virus, vaccinia, or, preferably, an RNA virus such as a retrovirus. Preferably, the retroviral vector is a derivative of a murine or avian retrovirus. Examples of retroviral vectors in which a single foreign gene can be inserted include, but are not limited to: Moloney murine leukemia virus (MoMuLV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), and Rous Sarcoma Virus (RSV). A number of additional retroviral vectors can incorporate multiple genes. All of these vectors can transfer or incorporate a gene for a selectable marker so that transduced cells can be identified and generated. By inserting a GDF-3 sequence of interest into the viral vector, along with another gene which encodes the ligand for a receptor on a specific target cell, for example, the vector is now target specific. Retroviral vectors can be made target specific by inserting, for example, a polynucleotide encoding a sugar, a glycolipid, or a protein. Preferred targeting is accomplished by using an antibody to targe the retroviral vector. Those of skill in the art will know of, or can readily ascertain without undue experimentation, specific polynucleotide sequences which can be inserted into the retroviral genome to allow target specific delivery of the retroviral vector containing the GDF-3 antisense polynucleotide.

Detailed Description Text (47):
Another targeted delivery system for GDF-3 antisense polynucleotides is a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. The preferred colloidal system of this invention is a liposome. Liposomes are artificial membrane vesicles which are useful as delivery vehicles in vitro and in vivo. It has been shown that large unilamellar vesicles (LUV), which range in size from 0.2-4.0 .mu.m can encapsulate a substantial percentage of an aqueous buffer containing large macromolecules. RNA, DNA and intact virions can be encapsulated within the aqueous interior and be delivered to cell in a biologically active form (Fraley, et al., Trends Biochem. Sci., 6:77, 1981). In addition to mammalian cells, liposomes have been used for delivery of polynucleotides in plant, yeast and bacterial cells. In order for a liposome to be an efficient gene transfer vehicle, the following characteristics should be present: 1

encapsulation of the genes of interest at high efficiency while not compromising their biological activity; 2) preferential and substantial binding to a target cell in comparison to non-target cells; 3) delivery of the aqueous contents of the vesicle to the target cell cytoplasm at high efficiency; and 4) accurate and effective expression of genetic information [Mannino, et al., Biotechniques, 6:682, 1988].